Perinatal Psychiatric Decision-Making: Deciphering the Data

Vivien K. Burt MD PhD
The Women’s Life Center
Resnick Neuropsychiatric Hospital at UCLA
March 2016

Disclosure:
Vivien K. Burt, MD, PhD

<table>
<thead>
<tr>
<th>Company</th>
<th>Advisory Board</th>
<th>Speaker’s Bureau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunovion</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Otsuka</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Takeda</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lundbeck</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Dr. Burt’s presentation will include discussion of commercial products not specifically approved for use in pregnancy or breastfeeding.
One Patient: Audrey’s Story

- My psychiatrist sent me for a second opinion by a perinatal psychiatrist.
- I’ve always been a worrier - even as a child.
- I’ve been pretty depressed in the past – worse after the birth of my daughter, three years ago. My antidepressant was very helpful, but I stopped it when I wanted to get pregnant again.
- I had a miscarriage one year ago, at 10 weeks gestation. I got depressed again, and so restarted my antidepressant.

Audrey’s Pre-Pregnancy Consultation

- My husband and I want to have another baby
- Should I stop my antidepressant?
- I want what’s is best for a baby and myself both during and after pregnancy.
- And I worry – I read so much about the risk of congenital malformations – and what about what I read about the risk for autism?
- Can I breast feed?
  - Is it safe to take medications when I am nursing?
  - What about sleep-deprivation?
  - What about my risk for postpartum depression?

Depression in Women of Childbearing age: Where Are We Now?
What We Know about Audrey

- 36 years old, married x 5 years, supportive husband
- Baseline anxious personality, worse when depressed
- 2 prior serious MDEs – all with neurovegetative signs/symptoms, impaired function
  - MDE#1 – age 32 – began third trimester – extended into postpartum, more obsessional/ruminative-treated with SSRI and psychotherapy
  - MDE#2 – age 35 – after miscarriage – treated with SSRI for 6 mos, tapered – restarted due to relapse.

More About Audrey

- Other pertinent issues
  - Mother - history of depression, postpartum depression
  - Supportive and loving husband, parents and in-laws
  - Financially stable
- Current Meds: an SSRI + prenatal vitamins
- Current condition:
  - Fully functional - No neurovegetative signs or symptoms
  - But ruminating/worrying re. ADs in pregnancy
  - Husband concerned as well
- MSE: well-related, neat, articulate, bright, normal weight, very worried, anxious, sad (in context), not clinically depressed, no psychotic sx or sx, insight/ judgment intact

This information includes a use that has not been approved by the US FDA.
What We Do in the Women’s Life Center

- For the therapeutic alliance to be therapeutic, no secrets
- What we know and what we think should be shared with the patient, referring health-care providers and significant others of her choosing.
- The patient should be offered ample opportunity to clarify assessment, case formulation, and treatment recommendations (based on the latest cited peer-reviewed evidence-based data)
- To achieve this, we have been providing patients their written evaluations.
- We provide added information as new data emerges

Basic Treatment Plan

- Team approach: patient, primary psychiatrist, perinatal consultant, therapist (recommended), husband, ob
- Continue SSRI at the minimum effective dose now, when pregnant, and during postpartum
- Psychotherapy to address miscarriage bereavement issues, to augment AD, to provide lifelong tools for anxiety
- Close psych f/u important

Basic Treatment Plan

- By gestational week 18, high resolution UTZ
- Postpartum: encourage surveillance for neonatal adaptive difficulties (in hospital for 48 hrs, if possible)
- BFing ok with SSRI, but with caveats: consider issue of sleep deprivation, consider availability of childcare help, consider supplemental formula feeding
**Discussion:**

Depression in Pregnancy: Negative Maternal Outcomes

- Inadequate weight gain
- Impaired sleep
- Overwhelmed, anxious
- Smoke, drink, use drugs
- Use multiple non-studied medications
- Ambivalent about pregnancy (even planned)
- Consider or elect abortion
- Risk increased for postpartum disorders
- Increased risk of premature birth, C-section, instrumental vaginal deliveries, IUGR, LBW, postnatal complications
- Increased risk for poorer neurobehavioral outcomes in babies

---

**Depression during pregnancy:**

“A child’s first adverse life event?”


---

**Sharing Information:**

What is the impact of Antidepressants in Pregnancy on the Infant?
Medications In Pregnancy: 
Risks To Consider

- Birth Defects
- Miscarriage
- Fetal health at delivery
- Growth impairment
- Longer-term impact

Reviewing the Literature: 
Let’s Start with One Issue - Cardiac Teratogenicity

Reading the Literature Critically with Our Patients and Our Colleagues

The Concept of “Confounding by Indication”

An Example: Malm et al Case Control Study:

- Finnish study, linked database - 635,583 mother-child pairs- (used recorded first trimester SSRI purchases)
- Findings:
  - SSRIs as a group and individually: No significant increase in risk for overall major malformations
  - However:
    - FLX increased VSD risk two-fold
    - Paroxetine increased right ventricular outflow defects five-fold
    - Citalopram increased neural tract defects 2 ½-fold
    - Risk of fetal alcohol spectrum disorders 10x higher in SSRI-exposed cases!
    - Examining subjects closely: Women who purchased SSRIs were less likely to be married, more likely to smoke/have chronic diseases/use non-SSRI psych meds and non-psych meds as well
  - Suggests underlying psychiatric condition was responsible for both SSRI and alcohol use → fetal alcohol spectrum disorders.

Malm et al: OB-Gyn 2011;118:111-20
Malm et al Case Control Study:

- Study suggests **confounding by indication** with depression may have predisposed to adverse outcome rather than SSRI itself.
- **Problem with study design:** SSRI-exposed depressed women were compared with unexposed non-depressed women.
- **Study that needs to be done:** Randomized control data where depressed women are randomized to SSRI or placebo – **but unethical in pregnancy**

*This is the problem with case control data-based linked studies.*

Another study: SSRIs & Cardiac Defects (Huybrechts 2014)

- Population-based cohort study, AHRQ/NIH study, Medicaid population, N=950,000 - **Propensity Matching**
- **Outcomes:**
  - Primary: Major cardiac malformations (MCMs) among first trimester AD-exposed infants versus non-exposed infants
  - Secondary: Types of cardiac defects
- **Method (Propensity matched):**
  - Pharmacy records (exposure = drugs supplied in first trimester)
  - Cardiac malformations recorded in maternal, infant records up to first 90 days postpartum
  - Recorded maternal depression diagnoses
- **Propensity matching:** To address severity of maternal depression – used proxies (pain-related disorders, sleep disorders, smoking, CFS, etc.)

Huybrechts et al. NEJM 2014;370:2397-407
Conclusion: Antidepressants and Risk for Cardiac Defects - (NEJM 2014)

- When adjusted for diagnosis of depression AND depressive-equivalent markers:
  - No statistically significant risk of any cardiac malformation with first trimester exposure to any antidepressants (SSRIs, SNRIs, bupropion)
  - SSRIs
    - No significant association between use of paroxetine and right ventricular outflow tract obstruction
    - No significant association between sertraline and ventricular septal defect

SSRI Antidepressants and Teratogenicity - what we discussed with Audrey and her husband

- SSRIs most studied ADs in pregnancy - >33,000 reported published exposures
- Overall SSRI use is not associated with specific congenital defects
- Note: background risk for major congenital malformations is 3%
- Any risk if it exists is very low, probably no more than 1/2500 births (.04%)

Other Issues to Consider

- No increased risk of miscarriage (Large systematic review and meta-analysis of pregnancy and delivery outcomes after exposure to antidepressants)
- No increased risk of stillbirth, neonatal mortality, post-neonatal mortality with antenatal SSRIs
- SSRIs and untreated maternal depression do not cause clinically significant lower birth weight.
- There is small statistically significant but probably not clinically significant reduction in length of gestation (about 3 days) with antidepressants and/or depression exposure in pregnancy
Neonatal Adaptability – 3rd Trimester Use of ADs

- Poor adaptability* (15-30%):
  - Transient perinatal adverse events*: jittery, muscle tone, resp distress, suck – mostly mild, transient
  - Infants exposed to antidepressants should be monitored after birth for 48 hours for additional care as needed.
- Prospective follow-up of affected infants:
  - no adverse impact on intelligence****, aberrant behaviors, depression, anxiety) at ages 4-5***
- 12/14/2011: FDA update: after review of different studies, "It is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN."
- Recommendation: FDA advises health care professionals not to alter their current clinical practice of treating depression during pregnancy.*


Reviewing the Literature:

Yet Another Issue - Autism

Reading the Literature Critically with Our Patients and Our Colleagues

SSRIs in pregnancy – autism association?

- Three case control studies:
  - Kaiser N. CA study (small study 298 cases + 1507 controls)
  - Swedish cohort study (larger study 4429 cases + 43,277 controls)
  - CHARGE California study (492 cases ASD + 154 DD + 320 controls)
- All tried to control for maternal age/education, other factors
- Suggested possible association between AD use in pregnancy and ASD
- Kaiser study found association only with SSRIs
- Swedish study found association with other ADs as well
- California study (CHARGE) found association with SSRIs for ASD, possible DD in boys
- Not enough to explain huge rise in ASD since the 1980’s (if true)
- Major problem with studies: confounding by indication.
If ADs increase ASD risk, this information must be told!

- Keep in mind:
  - Although studies do not prove that ADs increase ASD risk, women deciding whether or not to take ADs while pregnant understandably concerned.
  - Although case-control studies may identify associations, they often overestimate magnitude of risk
  - Depressed women more likely to smoke, drink alcohol, take illicit drugs (generally not controlled)
  - Apparent risk may actually be a result of confounding by indication.

- What we explained and discussed:
  - No study is perfect – all are subject to confounders – including presence and severity of maternal illness (i.e., confounding by indication)

Expectant mother’s health is important for health of mother and baby in pregnancy and the postpartum, and throughout the lives of mother and child.

What Happened

- Audrey continued her antidepressant, added CBT to address miscarriage concerns, other worries, fears, negative cognitions
- Three months after initial pre-pregnancy consultation Audrey became pregnant.
- Second trimester: High level UTZ – no sign of major organ malformation
  - **BUT**: Nuchal translucency – UPPER LIMITS OF NORMAL
  - Concern regarding heart defect
  - Patient became extremely anxious
  - CBT frequency increased to twice a week
  - Fetal echocardiogram performed at 22 weeks – normal

Further Into Second Trimester

- Weekly psychiatric visits:
  - Episodic dysphoria/irritability
  - Antidepressant dose adjusted to maintain efficacy
  - Note dilutional effect of antidepressant not uncommon
- By middle of second trimester:
  - Experienced fetal movements
  - Psychiatically stable
Revisiting Issue of Autism

- New large Danish registry study
- Data from >600,000 children born 1996-2006
  - Nearly 9000 prenatal exposures to SSRIs, over 6000 with maternal affective history
- Autism outcomes:
  - With prenatal SSRI ≈ 2%, without SSRI ≈ 1.5%
  - If data restricted to children of mothers with prenatal affective disorder: no statistically significant risk in ASD with prenatal SSRI exposure.
  - Comparing siblings with and without ASD, prenatal SSRI exposure not significant contributor to ASD risk
- Conclusion: After controlling for confounding factors, no significant association between prenatal SSRI exposure and ASD in offspring.


Revisiting Issue of Autism

- Second new Danish study also suggests no risk of ASD
- Large cohort study
  - 1996-2005 (flu through 2009)
- Found that SSRIs prior to pregnancy rather than during pregnancy was statistically significantly associated with increased ASD risk.
- Conclusion: any increased risk was due to confounding by indication rather than by effect of SSRIs – i.e., maternal depression, not ADs increase risk for ASD


And Then Yet Another Study on Autism and SSRIs in Pregnancy

- JAMA Pediatrics 2015: Boukhris et al
- Register based study of population-based cohort of infants born in Quebec between 1998 and 2009 (N=145000)
- 1.87 Hazard Risk in ASD IN SSRI-exposures in 2-3rd trimester vs. un exposed pregnancies
  - what was not addressed – severity of maternal depression during pregnancy – if women took ADs late in pregnancy, they were more likely to be seriously depressed (Confounded by Indication)
  - AND restricting study to children with ASD diagnosed by psychiatrist or neurologist result was not significant.
- Boukhris et al JAMA Pediatr 2015; Dec; 14. 1-8
And Here Were the Headlines

- **USA Today:** Taking antidepressants during pregnancy linked to increased risk of autism.
- **Huffington Post:** Major Study Links Autism To Antidepressant Use During Pregnancy
- **Science News:** “Taking antidepressants during pregnancy increases risk of autism by 87 percent”

So, yet another discussion with Audrey and her husband!

Sample Email from A Colleague......

- “Hi Vivien, Look at this article! Could you let me know how this information should impact our recommendations for pts who are on SSRIs in pregnancy? You know, there isn’t a PCP around who will want their pts on an SSRI in pregnancy. Happy Holidays.”

- Dear Vivien, I have read the article in question closely. I am always amazed at how even reputable and esteemed journals can publish articles with abstracts that are scary and misleading and will get into widespread press... In my opinion (which I will discuss at tomorrow’s Women’s Life Center conference) the conclusion that late trimester use of SSRIs increase risk of ASD is misleading and flawed for many reasons – the most important is that it is confounded by indication. I am enclosing more specific comments enumerating flaws as an attachment.

- “Thanks Vivien. The problem is that I would very much like pts to stay on their SSRIs, but the mention of ASD makes everyone panic – and that includes my patients and ME!”
**Third Trimester**

- **Decision**: Continue antidepressant at efficacious dose
  - Discussed with OB, who agreed that psych stabilization high priority
  - Pediatrician will follow closely
- Psych status: stable
- 37 weeks: Healthy baby boy delivered - NVD
  - 3500 grams (7.7 pounds)
  - APGARS: 7/8

**Postpartum**

- Shortly after birth:
  - Transient tachypnea, occasional jerking
  - Baby placed in NICU for observation – stabilized rapidly
- Twelve hours’ postpartum
  - Baby returned to mother’s room
  - No breathing difficulties
- 36 hours’ postpartum
  - Baby fully normalized

**Postpartum**

- Patient continued antidepressant, CBT
- Mother-in-law and mother provided additional daytime assistance with older child and baby three afternoons a week for first three months
- Breast-fed for three months with supplemental feedings (discussion regarding safety of antidepressant reviewed with patient)
  - Weaned after three months due to effects of sleep deprivation
  - CBT helped Audrey appreciate breastfeeding she accomplished, while not blaming herself for stopping at 3 months!
Postpartum – 6 Months

- Meds: Continued antidepressant, CBT
- Baby meeting all developmental milestones
- Audrey relaxed and delighted with her family
- Felt competent and able to care for two children
  - But tired, so got babysitter three afternoons a week; husband took over one night-time feeding and one weekend afternoon child care
- Plan: continue antidepressant for first postpartum year, then taper slowly, under psychiatric care
- Continue CBT, reduced to twice a month.
- Birth control – IUD in place. No further plans for pregnancy

Essential Take-Home Messages

- Carefully consider patient’s history:
  - Previously had demonstrated stability on SSRI
  - Psychotherapy helpful in the past
  - Changing need for medication in pregnancy
    - Dose changes of sertraline, addition of lorazepam
- Anticipate complications – address calmly and openly with all concerned (patient, family, providers):
  - Miscarriage – psychological residue
  - Concern about heart defect
  - Neonatal adaptive difficulties – short term
  - Breast-feeding
  - Childcare

Sharing Our Guiding Principles with Audrey and Her Husband

- Overall health of expectant mother is important for mother and fetus
- Depression during pregnancy increases risk of postpartum depression
- Risk of untreated illness must be balanced against risk of antidepressants on mother and baby
- Best time to organize a treatment plan is before pregnancy!
- Remember: What drives the media - “What Bleeds Leads”. Interpreting the literature is not easy and is key to understanding risks and benefits.
Some Quotes that Have Helped Me

- **Maya Angelou**: You did what you knew how to do. And when you knew better, you did better.

- **Arthur Ashe**: Start where you are. Use what you have. Do what you can.

- **Someone special**: Nothing is perfect. If you expect perfection then you will be disappointed and unhappy.

The Goal: Keeping Mothers and Their Babies Well: Screen, Diagnose, Treat